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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 032219WOTM	**FOR FURTHER ACTION** See Form PCT/IPEA/416	
International application No. PCT/HU2004/000077	International filing date *(day/month/year)* 16.07.2004	Priority date *(day/month/year)* 16.07.2003
International Patent Classification (IPC) or national classification and IPC A61K31/42, C07D231/12		
Applicant RICHTER GEDEON VEGYESZETI GYAR RT.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
11.05.2005	23.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Molina de Alba, J Telephone No. +49 89 2399-7823

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/HU2004/000077

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-18 as originally filed

Claims, Numbers

1-14 received on 12.05.2005 with letter of 11.05.2005

Drawings, Sheets

1/3-3/3 as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	13,14?

2. Citations and explanations (Rule 70.7):

see separate sheet

The amendments filed by the Applicant with letter of 11.05.2005 fulfil the requirements of Art. 19(2) PCT in that they do not extend beyond the content of the application as originally filed.

The application relates now to *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide solvates, as well as to the preparation and therapeutical uses thereof for the treatment of osteoarthritis, rheumatoid arthritis and surgical and primary dysmenorrheal pains.

Reference is made to the following documents:

D1: JOSH J. YUAN ET AL.: "Disposition of a specific cyclooxygenase-2 inhibitor, valdecoxib, in human" DRUG METABOLISM AND DISPOSITION, vol. 30, no. 9, 2002, pages 1013-1021, XP002311618

D2: JOHN J. TALLEY ET AL.: "4-[5-Methyl-3-phenylisoxazol-4-yl]-benzen esulfonamide, Valdecoxib: A potent and selective inhibitor of COX-2" J.MED.CHEM., vol. 43, 2000, pages 775-777, XP002311619

Re Item V

Novelty (Art. 33(2) PCT)

Document **D1** states (cf. abstract, and Fig. 5) that the primary oxidative metabolic pathway of valdecoxib involves hydroxylation at either the methyl group to form M1 or *N*-hydroxylation at the sulfonamide moiety to form M2 (*N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide). Both metabolites were identified: pg. 1018, col. 1, par. 2 and pg. 1018, col. 2, par. 2. In particular, M2 was synthesized as standard for comparison with the isolated metabolite and its glucuronide conjugate was studied by CID and NMR (cf. also fig. 8 and 10). Nevertheless, **D1** does not describe a **solvate form** of M2. The claimed subject-matter is therefore novel over **D1**.

Inventive Step (Art. 33(3) PCT)

D2 is regarded as the closest state of the art. This document shows (cf. pg. 776, col. 2, par. 2-3) that valdecoxib and its metabolite resulting from oxidation at the methyl group are

selective and potent inhibitors of COX-2. The presently claimed compounds, compositions, uses and methods differ from **D2** in that the substance involved is **another primary metabolite of valdecoxib obtained by oxidation**. The problem to be solved by the application may thus be regarded as providing **alternative** compounds, compositions, uses, and methods to those disclosed in **D2**.

D1 (cf. Fig. 5) shows *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide (M2) as one of the three primary metabolites obtained by oxidation of valdecoxib (the compound of **D2** is another one of these three metabolites).

Even though the skilled person in the search of alternative compounds to valdecoxib would likely test the metabolite *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide as a suitable candidate, in the expectation of achieving results comparable to those provided by valdecoxib or its corresponding metabolite tested in **D2**, no hint has been found in the prior art which would incite the skilled person to test the compound in its **solvate form**. Furthermore, the fact that the solvate form of *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide exhibits an unexpected stability, that it provides a comparable or, in the case of a chronic model, even better activity than valdecoxib, and that it significantly improves the vascular bed of the heart, is regarded as a basis for the acknowledgement of an inventive step.

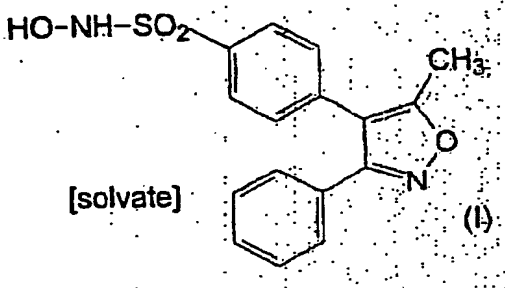
Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-12

For the assessment of the present claims 13 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Claims

1. N-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide solvates of formula (I)



(I)

wherein [solvate] represents water, C_1-C_4 alcohol, C_1-C_4 alkylester of C_1-C_3 carboxylic acid or dioxane.

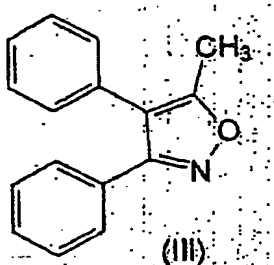
2. A compound of formula (I) as claimed in Claim 1, wherein the solvate represents water.

3. A compound of formula (I) as claimed in Claim 1, wherein the solvate represents ethylacetate.

4. A compound of formula (I) as claimed in Claim 1, wherein the solvate represents 2-propanol.

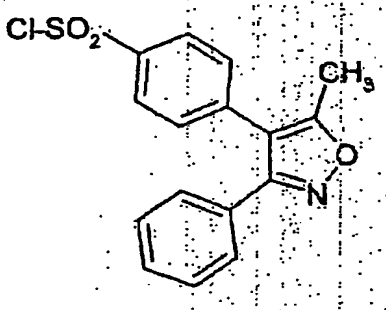
5. A compound of formula (I) as claimed in Claim 1, wherein the solvate represents dioxane.

6. Process for producing N-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide solvates compounds of formula (I) wherein solvate represents C_1-C_4 alkylester of C_1-C_3 carboxylic acid or dioxane, characterized by that the 3,4-diphenyl-5-methyl-izoxazole of formula (III)



(III)

is reacted with chlorosulfonic acid and the product 3-phenyl-4-(4-chlorosulfonyl-phenyl)-5-methyl-isoxazole (II)



(II)

is reacted with hydroxylamine

a.) in mixture of water and water miscible solvent or

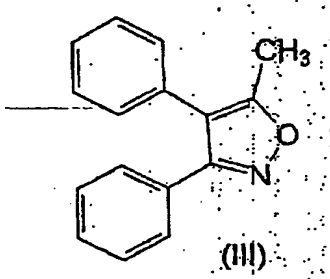
b.) in mixture of non-water-miscible solvent and water in presence of phase transfer catalyst,

and the product is crystallized from a solvent chosen from a C_1-C_4 alkylester of C_1-C_3 carboxylic acid or dioxane.

7. Process as claimed in Claim 6 characterized by that the phase-transfer catalyst is tetrabutylammonium hydrogensulfate.

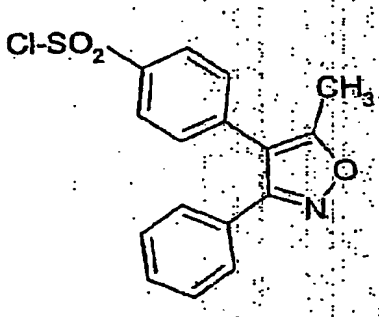
8. Process as claimed in Claim 6 characterized by that the recrystallization was carried out from ethyl acetate.

9. Process for producing N-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide solvate compounds of formula (I) wherein solvate represents water, characterized by that the 3,4-diphenyl-5-methyl-izoxazole of formula (III)



(III)

is reacted with chlorosulfonic acid and the product 3-phenyl-4-(4-chloro-sulfonyl-phenyl)-5-methyl-isoxazole (II)



(II)

is reacted with hydroxylamine

a.) in mixture of water and water miscible solvent or

b.) in mixture of non-water-miscible solvent and water in presence of phase transfer catalyst,

and the product is crystallized from a mixture of water and ethanol, optionally containing ascorbic acid.

10. Use of compounds of formula (I) claimed in any of Claims 1-5 for producing pharmaceutical composition for treatment of osteoarthritis and rheumatoid arthritis and surgical and primary dysmenorrheal pains.

11. Pharmaceutical composition containing a compound of formula (I) as claimed in any of Claims 1-5 and one or more therapeutically acceptable pharmaceutical carriers.

12. Pharmaceutical composition as claimed in Claim 11 characterized by that the one of the carriers is ascorbic acid.

13. A method for treatment of osteoarthritis and rheumatoid arthritis and surgical and primary dysmenorrheal pains comprising treating the patient in need with therapeutically effective dose of a compound of formula (I) as claimed in any of Claims 1-5.

14. A method for treatment of osteoarthritis and rheumatoid arthritis and surgical and primary dysmenorrheal pains comprising treating the patient in need with therapeutically effective dose of a pharmaceutical composition as claimed in any of Claims 11-12.